

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 December 1996 (02.12.96)	
International application No. PCT/US96/04407	Applicant's or agent's file reference TJU-1836
International filing date (day/month/year) 28 March 1996 (28.03.96)	Priority date (day/month/year) 28 March 1995 (28.03.95)
Applicant PROCKOP, Darwin, J. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
25 October 1996 (25.10.96)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Marie-José Devillard

Telephone No.: (41-22) 730.91.11

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 27 MAY 1997

WIPO PCT

Applicant's or agent's file reference TJU-1835	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US96/04407	International filing date (day/month/year) 28 MARCH 1996	Priority date (day/month/year) 28 MARCH 1995
International Patent Classification (IPC) or national classification and IPC IPC(6): A61K 35/14, 35/28 and US Cl.: 424/93:7, 529, 577		
Applicant THOMAS JEFFERSON UNIVERSITY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 25 OCTOBER 1996	Date of completion of this report 06 MAY 1997
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEAN C. WITZ Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/04407

I. Basis of the report

1. This report has been drawn on the basis of (*Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments*):

☒ the international application as originally filed.

☒ the description, pages 1-50, as originally filed.

pages NONE, filed with the demand.

pages NONE, filed with the letter of _____.

pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-54, as originally filed.

Nos. NONE, as amended under Article 19.

Nos. NONE, filed with the demand.

Nos. NONE, filed with the letter of _____.

Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/~~fig~~ 1-2, as originally filed.

sheets/~~fig~~ NONE, filed with the demand.

sheets/~~fig~~ NONE, filed with the letter of _____.

sheets/~~fig~~ _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE.

☒ the claims, Nos. NONE.

☒ the drawings, sheets/~~fig~~ NONE.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/04407

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 5 and 12-38

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _ are so unclear that no meaningful opinion could be formed (*specify*).

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 5 and 12-38.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/04407

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>1-4, 6-11, 39-54</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-4, 6-11, 39-54</u>	NO
Industrial Applicability (IA)	Claims <u>1-4, 6-11, 39-54</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-4, 6-11 and 39-54 lack an inventive step under PCT Article 33(3) as being obvious over Coccia et al., Piersma et al., Niedzwiedski et al., Wakitani et al., Nakagawa et al., Itay and Castro-Malaspina et al.

The claims are drawn to the therapeutic treatment of an individual suffering from a disease, disorder or condition characterized by a defect in bone, cartilage or lung with intravenous injection of bone marrow stromal cells.

Coccia et al. disclose that a five-month old girl with osteopetrosis, a congenital bone disorder, was successfully treated with an intravenous infusion of bone marrow from her brother following bone marrow ablation. Y chromosomes were identified in osteoclasts after transplantation. The reference does not disclose isolating the adherent stromal cells, but administers a composition of bone marrow aspirate known to include stromal cells (see page 298, second column of Castro-Malaspina et al., discussed infra).

Piersma et al. disclose that stromal cells can be transplanted via the intravenous route and establish themselves in the hematopoietic environment. The reference does not disclose the treatment of any condition with bone, cartilage or lung defect.

Niedzwiedski et al. disclose that bone marrow stromal cells are osteogenic when implanted into the area of a bone defect. Similarly, Wakitani et al. disclose that bone marrow stromal cells can repair articular cartilage when implanted into cartilaginous defects. Neither reference discloses intravenous injection.

Nakagawa et al. disclose that polyarthritis in male mice was treated by intravenously injected bone marrow cells and bone (to recruit stromal cells). Stromal cells were deemed essential in supporting the bone marrow cells and preventing graft failure.

(Continued on Supplemental Sheet.)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/04407

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Applicants have not provided any evidence regarding the treatment of conditions of the lung which may be treated in this manner, specifically conditions such as cystic fibrosis. It remains unclear and unpredictable that a repopulation of approximately 5% or less of these cells in lungs of the recipient will provide any therapeutic benefit to such conditions, especially as 95% or more of the cells in the lungs either express or fail to express genes which are responsible for the conditions of the lung.

Claims 1-4, 6-11 and 39-54 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US96/04407

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

~~Sheet 10~~**V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):**

Itay discloses treating bone or cartilage defects by implanting bone marrow progenitor cells from bone marrow, specifically bone marrow stromal cells. See column 5, lines 40-43.

Finally, Castro-Malaspina et al. disclose that bone marrow stromal cells contain fibroblast colony-forming cells which produced fibroblast progeny.

In view of the teaching of the prior art references taken as a whole, it would have been obvious to treat a condition of bone or cartilage with an intravenous infusion of bone marrow stromal cells because the practitioner would 1) the bone marrow stromal cells would engraft at the marrow site (per Piersma), 2) would produce fibroblast cells, and ultimately osteoblast and chondroblast cells (per Niedzwiedski, Wakitani, Castro-Malaspina, Itay and Nakagawa, and 3) which would migrate to bone and cartilage adjacent the marrow sites to produce new bone and/or cartilage as evidenced by the showing of Coccia and Nakagawa.

----- NEW CITATIONS -----

NONE

PATENT COOPERATION TREATY

PSJ/mj

RECEIVED

From: **INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY**

To: **PHILIP S. JOHNSON
WOODCOCK, WASHBURN, KURTZ, MACKIEWICZ
& NORRIS
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103**

PCT MAY 21 1997

**NOTIFICATION OF TRANSMITTAL OF
INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

(PCT Rule 71.1)

Date of Mailing
(day/month/year)

16 MAY 1997

Applicant's or agent's file reference

TJU-1835

IMPORTANT NOTIFICATION

International application No.

PCT/US96/04407

International filing date (day/month/year)

28 MARCH 1996

Priority Date (day/month/year)

28 MARCH 1995

Applicant

THOMAS JEFFERSON UNIVERSITY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JEAN C. WITZ

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PST/md ✓

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: PHILIP S. JOHNSON
WOODCOCK, WASHBURN, KURTZ, MACKIEWICZ &
NORRIS
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

RECEIVED PCT

FEB 13 WRITTEN OPINION

WOODCOCK WASHBURN (PCT Rule 66)
KURTZ MACKIEWICZ & NORRIS

Date of Mailing
(day/month/year)

10 FEB 1997

Applicant's or agent's file reference

TJU-1835-1836

REPLY DUE

within TWO months
from the above date of mailing

International application No.

PCT/US96/04407

International filing date (day/month/year)

28 MARCH 1996

Priority date (day/month/year)

28 MARCH 1995

International Patent Classification (IPC) or both national classification and IPC
IPC(6): A61K 35/14, 35/28 and US Cl.: 424/93.7, 529, 577

Applicant

THOMAS JEFFERSON UNIVERSITY

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 28 JULY 1997

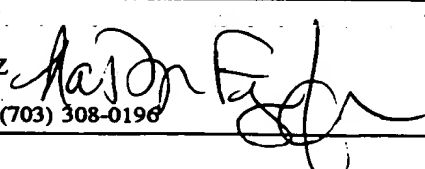
Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile N (703) 305-3230

Authorized officer

JEAN C. WITZ

Telephone No. (703) 308-0196



WRITTEN OPINION

International application No.

PCT/US96/04407

I. Basis of the opinion

1. This opinion has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

☒ the international application as originally filed.

☒ the description, pages 1-50 , as originally filed.

pages NONE , filed with the demand.

pages NONE , filed with the letter of _____.

☒ the claims, Nos. 1-54 , as originally filed.

Nos. NONE , as amended under Article 19.

Nos. NONE , filed with the demand.

Nos. NONE , filed with the letter of _____.

☒ the drawings, sheets/fig 1-2 , as originally filed.

sheets/fig NONE , filed with the demand.

sheets/fig NONE , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

WRITTEN OPINION

International application No.
PCT/US96/04407

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 5 and 12-38

because:

- ☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination (*specify*).

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _ are so unclear that no meaningful opinion could be formed (*specify*).

- ☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 5 and 12-38.

WRITTEN OPINION

International application No.

PCT/US96/04407

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	<u>1-4, 6-11, 39-54</u>	YES
	Claims	<u>NONE</u>	NO
Inventive Step (IS)	Claims	<u>NONE</u>	YES
	Claims	<u>1-4, 6-11, 39-54</u>	NO
Industrial Applicability (IA)	Claims	<u>1-4, 6-11, 39-54</u>	YES
	Claims	<u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-4, 6-11 and 39-54 lack an inventive step under PCT Article 33(3) as being obvious over Coccia et al., Piersma et al., Niedzwiedski et al., Wakitani et al., Nakagawa et al., Itay and Castro-Malaspina et al.

The claims are drawn to the therapeutic treatment of an individual suffering from a disease, disorder or condition characterized by a defect in bone, cartilage or lung with intravenous injection of bone marrow stromal cells.

Coccia et al. disclose that a five-month old girl with osteopetrosis, a congenital bone disorder, was successfully treated with an intravenous infusion of bone marrow from her brother following bone marrow ablation. Y chromosomes were identified in osteoclasts after transplantation. The reference does not disclose isolating the adherent stromal cells, but administers a composition of bone marrow aspirate known to include stromal cells (see page 298, second column of Castro-Malaspina et al., discussed infra).

Piersma et al. disclose that stromal cells can be transplanted via the intravenous route and establish themselves in the hematopoietic environment. The reference does not disclose the treatment of any condition with bone, cartilage or lung defect.

Niedzwiedski et al. disclose that bone marrow stromal cells are osteogenic when implanted into the area of a bone defect. Similarly, Wakitani et al. disclose that bone marrow stromal cells can repair articular cartilage when implanted into cartilaginous defects. Neither reference discloses intravenous injection.

Nakagawa et al. disclose that polyarthritis in male mice was treated by intravenously injected bone marrow cells and bone (to recruit stromal cells). Stromal cells were deemed essential in supporting the bone marrow cells and preventing graft failure.

(Continued on Supplemental Sheet.)

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-4, 6-11 and 39-54 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because practice of the claimed invention is not enabled as required under PCT Rule 5.1(a) for the reasons set forth in the immediately preceding paragraph.

Applicants have not provided any evidence regarding the treatment of conditions of the lung which may be treated in this manner, specifically conditions such as cystic fibrosis. It remains unclear and unpredictable that a repopulation of approximately 5% or less of these cells in lungs of the recipient will provide any therapeutic benefit to such conditions, especially as 95% or more of the cells in the lungs either express or fail to express genes which are responsible for the conditions of the lung.

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Itay discloses treating bone or cartilage defects by implanting bone marrow progenitor cells from bone marrow, specifically bone marrow stromal cells. See column 5, lines 40-43.

Finally, Castro-Malaspina et al. disclose that bone marrow stromal cells contain fibroblast colony-forming cells which produced fibroblast progeny.

In view of the teaching of the prior art references taken as a whole, it would have been obvious to treat a condition of bone or cartilage with an intravenous infusion of bone marrow stromal cells because the practitioner would 1) the bone marrow stromal cells would engraft at the marrow site (per Piersma), 2) would produce fibroblast cells, and ultimately osteoblast and chondroblast cells (per Niedzwiedski, Wakitani, Castro-Malaspina, Itay and Nakagawa, and 3) which would migrate to bone and cartilage adjacent the marrow site to produce new bone and/or cartilage as evidenced by the showing of Coccia and Nakagawa.

----- NEW CITATIONS -----

NONE



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 35/14, 35/28		A1	(11) International Publication Number: WO 96/30031
			(43) International Publication Date: 3 October 1996 (03.10.96)
(21) International Application Number: PCT/US96/04407 (22) International Filing Date: 28 March 1996 (28.03.96) (30) Priority Data: 08/412,066 28 March 1995 (28.03.95) US 60/006,627 13 November 1995 (13.11.95) US (60) Parent Applications or Grants (63) Related by Continuation US 08/412,066 (CIP) Filed on 28 March 1995 (28.03.95) US 60/006,627 (CIP) Filed on 13 November 1995 (13.11.95) (71) Applicant (for all designated States except US): THOMAS JEFFERSON UNIVERSITY [US/US]; 11th and Walnut Streets, Philadelphia, PA 19107 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): PROCKOP, Darwin, J. [US/US]; 291 Locust Street, Philadelphia, PA 19106 (US). PEREIRA, Ruth, F. [IN/US]; 2nd floor, 101 E. Baltimore Avenue, Lansdowne, PA 19050 (US). LEEPER, Dennis, B. [US/US]; 21 Meredith Road, Wynnewood, PA 19096 (US).		O'HARA, Michael, D. [US/US]; 6 Underwood Road, Wyncote, PA 19095 (US). KULKOSKY, Joseph [US/US]; 6731 Martins Mull Road, Philadelphia, PA 19111 (US). PHINNEY, Donald [US/US]; 1841 Webster Lane, Maple Glen, PA 19002 (US). LAPTEV, Alexey [RU/US]; Apartment 1-F, 917 Pine Street, Philadelphia, PA 19107 (US). CARO, Jose [US/US]; 1227 Lafayette Road, Gladwyn, PA 19035 (US). (74) Agents: JOHNSON, Philip, S. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: ISOLATED STROMAL CELLS AND METHODS OF USING THE SAME			
(57) Abstract			
<p>Methods of treating patients who are suffering from a disease, disorder or condition characterized by a bone cartilage or lung defect are disclosed. The methods comprising the step of intravenous administration of stromal cells isolated from normal syngeneic individuals or intravenous administration of stromal cells isolated from the patient subsequent to correction of the genetic defect in the isolated cells. Implant devices comprising a container that has at least one membrane surface and stromal cells isolated from bone marrow that comprise a gene construct are disclosed. The gene construct in the stromal cells comprises a nucleotide sequence that encodes a beneficial protein operably linked to regulatory elements which function in stromal cells. Methods of treating individuals with diseases, disorders or conditions which can be treated with a beneficial protein, including diseases, disorders or conditions characterized by gene defects are disclosed. The methods comprise introducing into such individuals, stromal cells that are administered in a manner that physically isolates them from the recipient's immune system and that comprise a gene construct that comprises a nucleotide sequence that encodes a beneficial protein operably linked to regulatory elements which function in stromal cells.</p>			

INTERNATIONAL SEARCH REPORT

international application No.
PCT/US96/04407

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 35/14, 35/28

US CL : 424/93.7, 529, 577

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.7, 529, 577

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CA, BIOSIS, MEDLINE, DIALOG

search terms: bone marrow stromal cells, infusion or injection

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	COCCIA, P.F. et al. Successful bone-marrow transplantation for infantile malignant osteopetrosis. The New England Journal of Medicine. 27 March 1980, Vol. 302, No. 13, pages 702-707, see entire document.	1-4, 6-11, 39-54
Y	NAKAGAWA, T. et al. Prevention of autoimmune inflammatory polyarthritis in male New Zealand black/KN mice by transplantation of bone marrow cells plus bone (stromal cells). Arthritis and Rheumatism. February 1993, Vol. 36, No. 2, pages 263-268, see entire document.	1-4, 6-11, 39-54



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 JULY 1996

Date of mailing of the international search report

23 JUL 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JEAN C. WITZ

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/04407

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PIERSMA, A.H. et al. Transplantation of bone marrow fibroblastoid stromal cells in mice via the intravenous route. British Journal of Haematology. 1983, Vol. 54, pages 285-290, see entire document.	1-4, 6-11, 39-54
Y	NIEDZWIEDZKI, T. et al. Bone healing after bone marrow stromal cell transplantation to the bone defect. Biomaterials. 1993, Vol. 14, No. 2, pages 115-121, see entire document.	1-4, 6-11, 39-54
Y	WAKITANI, S. et al. Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. The Journal of Bone and Joint Surgery. April 1994, Vol. 76-A, No. 4, pages 579-592, see entire document.	1-4, 6-11, 39-54
Y	CASTRO-MALASPINA, H. et al. Characterization of human bone marrow fibroblast colony-forming cells (CFU-F) and their progeny. Blood. August 1980, Vol. 56, No. 2, pages 289-301, see entire document.	1-4, 6-11, 39-54
Y	US 4,904,259 A (ITAY) 27 February 1990 (27.02.90), see the abstract.	1-4, 6-11, 39-54

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/04407

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-4, 6-11 and 39-54

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-4, 6-11, and 39-54, drawn to a method of treating a patient with an intravenous infusion of bone marrow stromal cells.

Group II, claims 5 and 12-21, drawn to a method of treating a patient for a genetic defect with an intravenous infusion of genetically altered bone marrow stromal cells.

Group III, claims 22-27, drawn to an implant device containing genetically altered bone marrow stromal cells.

Group IV, claims 28-38, drawn to a method of treating a patient with an implant device containing stromal cells containing a gene construct which produces a beneficial protein.

The inventions listed as Groups I-IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The invention of group I is drawn to treating a patient by intravenous infusion of bone marrow cells. This is a technique which is well established in the art and has been used for many years (Coccia et al., The New England Journal of Medicine, 1980). Thus, treatment of genetic disorders using bone marrow stromal cells cannot be considered a special technical feature. The invention of group II is a second method. The invention of group III is a first product, unrelated to the method of group I. The invention of group IV is a third method. Accordingly, the claims are not so linked by a special technical feature within the meaning of PCT Rule 13.2 so as to form a single inventive concept.